Efficacy of Dolutegravir (DTG) Plus Lamivudine (3TC) Versus DTG Plus Tenofovir/Emtricitabine (TDF/FTC) in Antiretroviral Treatment-Naive Adults With HIV-1 Infection: 48-Week Subgroup Results From the GEMINI Studies in Latin American Participants

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Background

- The requirement for lifelong antiretroviral therapy of HIV infection has highlighted interest in 2-drug regimens (2DRs) to minimize cumulative drug exposure
- In the GEMINI-1/-2 studies, the 2DR of dolutegravir (DTG) plus lamivudine (3TC) was recently shown to be noninferior at Week 48 compared with the 3-drug regimen DTG + tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) in achieving plasma HIV-1 RNA <50 c/mL in treatment-naive adults[1]

Methods

- GEMINI-1 and GEMINI-2 are identically designed, double-blind, multicenter, phase III studies evaluating the efficacy and safety of once-daily DTG + 3TC in treatment-naive adults with HIV-1 infection and screening HIV-1 RNA ≥1000 and ≤500,000 c/mL[1]
- Participants were randomized 1:1 to DTG + 3TC or DTG + TDF/FTC and stratified by screening plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3)
- Eligibility criteria included ≤10 days of prior antiretroviral therapy, no evidence of preexisting viral resistance based on the presence of any major resistance-associated mutation, and no hepatitis B virus infection or need for hepatitis C therapy
- The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 (snapshot algorithm; intention-to-treat–exposed [ITT-E] population), with a 10% margin for noninferiority
- A post hoc analysis was conducted to look at outcomes in participants recruited from Latin American centers

Results

- A total of 1433 adults were randomized and treated across the 2 GEMINI studies, including 307 (21%) participants treated at 18 sites from 3 Latin American countries (Argentina, Mexico, Peru; Table 1)
- In the Latin American subset, 17% (26/152) of participants randomized to DTG + 3TC and 12% (18/155) randomized to DTG + TDF/FTC were female, and the median age was 31 years and 32 years, respectively
  - In the Latin American subgroup, 18% (28/152) and 24% (37/155) randomized to DTG + 3TC and DTG + TDF/FTC, respectively, had plasma HIV-1 RNA >100,000 c/mL at screening, and 9% (13/152) and 8% (12/155), respectively, had CD4+ cell count ≤200 cells/mm^3

Table 1. Demographics and Clinical Baseline Characteristics for the Pooled ITT-E Population

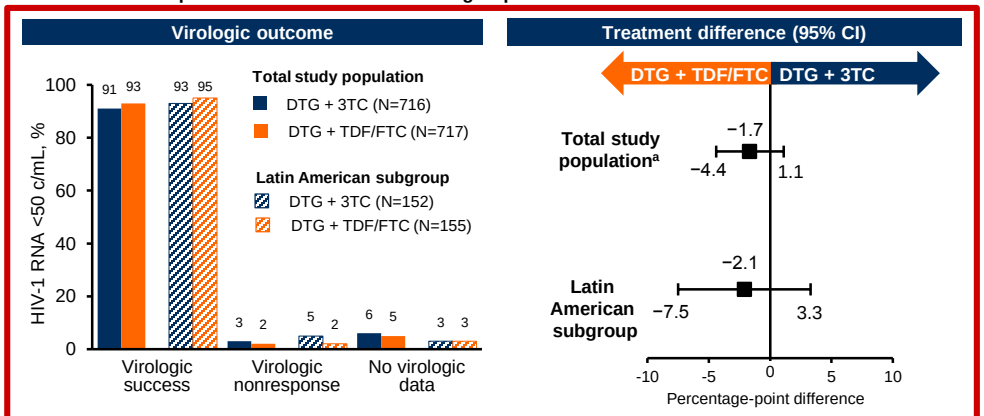
Demographic/Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic/Latino	215 (30)	232 (32)
Not Hispanic/Latino	501 (70)	485 (68)
Country, n (%)		
Argentina	91 (13)	91 (13)
Mexico	50 (7)	52 (7)
Peru	11 (2)	12 (2)
HIV-1 RNA, median (range), $\log_{10}$ c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
>100,000[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
≤200	63 (9)	55 (8)

[a]2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL and were included in the ITT-E analysis.

Snapshot Outcomes and Analysis at Week 48

- In the total study population, the efficacy of DTG + 3TC was noninferior to DTG + TDF/FTC at Week 48 (snapshot; ITT-E population; Figure)
- In the Latin American subgroup, responses were high and generally consistent with the total study population, noting the small patient numbers in individual countries
  - Responses were generally consistent in Latin American countries, although patient numbers were small in individual countries

Figure. Proportion of Participants by Virologic Response and Adjusted Treatment Difference (95% CI) for Pooled ITT-E Population and Latin American Subgroup



Snapshot Analysis

	Argentina		Mexico		Peru	
	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC	DTG + 3TC	DTG + TDF/FTC
Snapshot responders, % (n/N)	93 (85/91)	97 (88/91)	94 (47/50)	92 (48/52)	82 (9/11)	92 (11/12)
Unadjusted difference (95% CI)	−3.3 (−9.6, 3.0)		1.7 (−8.1, 11.5)		−9.8 (−37.5, 17.8)	

[a]Adjusted treatment difference based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm^3).

Virologic Outcomes Stratified by Baseline CD4+ Cell Count

- In the total study population, response rates among participant subpopulations defined by demographic and baseline characteristics were generally consistent with the overall response rate; an exception is the subpopulation of participants with baseline CD4+ counts ≤200 cells/mm^3
  - In both treatment groups, 93% of participants with CD4+ counts >200 cells/mm^3 achieved virologic suppression (HIV-1 RNA <50 c/mL; DTG + 3TC, n/N=605/653; DTG + TDF/FTC, n/N=618/662)[1]
    - In a post hoc analysis of participants who discontinued the study drug because of treatment failure (treatment-related discontinuation = failure [TRDF]), 99% (n/N=138/140) in the DTG + 3TC group and 97% (n/N=149/153) in the DTG + TDF/FTC group with baseline HIV-1 RNA >100,000 c/mL did not have TRDF
  - In participants with CD4+ counts ≤200 cells/mm^3, 79% (n/N=50/63) who received DTG + 3TC achieved HIV-1 RNA <50 c/mL compared with 93% (n/N=51/55) of those who received DTG + TDF/FTC[1]
    - Most reasons for snapshot failures (participants not achieving HIV-1 RNA <50 c/mL at Week 48) for this subgroup were unrelated to efficacy or treatment failure
    - In the post hoc TRDF analysis, 98% of participants with baseline CD4+ cell >200 cells/mm^3 in both treatment groups (DTG + 3TC, n/N=642/653; DTG + TDF/FTC, n/N=647/662) did not have TRDF
- Overall, 10 participants (DTG + 3TC, 6; DTG + TDF/FTC, 4) met the prespecified confirmed virologic withdrawal (CVW) criteria through Week 48 and were classified as virologic rebounds
  - None of the samples evaluated demonstrated the emergence of mutations associated with resistance to INSTIs or NRTIs

Bone and Renal Biomarkers at Week 48: Pooled ITT-E Population

- In the total study population, changes in renal and bone biomarkers were generally favorable in the DTG + 3TC group compared with the DTG + TDF/FTC group[1]

Safety Analysis

- Adverse event (AE) rates were similar between arms and between the Latin American subgroup and overall study population, with low rates of AEs leading to withdrawal (Table 2)
  - In the Latin American subgroup, drug-related AEs occurred in 24% and 30% of participants in the DTG + 3TC and DTG + TDF/FTC group, respectively, compared with 18% and 24%, respectively in the overall study population
  - In the Latin American subgroup, low rates of AEs leading to withdrawal were observed at Week 48 (2 participants per treatment arm [1%]) and were consistent with the overall study population

Table 2. Adverse Events in the Pooled ITT-E Population

	Latin America		Total study population	
n, %	DTG + 3TC (N=152)	DTG + TDF/FTC (N=155)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE, n (%)	113 (74)	130 (84)	543 (76)	579 (81)
AE occurring in >5% of participants in either group				
Headache	28 (18)	24 (15)	71 (10)	75 (10)
Diarrhea	21 (14)	30 (19)	68 (9)	77 (11)
Pharyngitis	21 (14)	15 (10)	36 (5)	32 (4)
Nasopharyngitis	13 (9)	21 (14)	55 (8)	78 (11)
Upper respiratory tract infection	9 (6)	5 (3)	56 (8)	44 (6)
Nausea	10 (7)	14 (9)	27 (4)	53 (7)
Insomnia	10 (7)	12 (8)	27 (4)	45 (6)
Back pain	9 (6)	8 (5)	35 (5)	31 (4)
Bronchitis	11 (7)	6 (4)	28 (4)	21 (3)
Influenza	12 (8)	5 (3)	22 (3)	28 (4)
Pharyngotonsillitis	6 (4)	9 (6)	6 (1)	11 (2)
Arthralgia	3 (2)	10 (6)	15 (2)	26 (4)
Gastroenteritis	4 (3)	8 (5)	17 (2)	22 (3)
Drug-related AE	37 (24)	47 (30)	126 (18)	169 (24)
Grade 2-5 AE occurring in ≥1% of participants	6 (4)	4 (3)	42 (6)	47 (7)
Headache	3 (2)	2 (1)	8 (1)	8 (1)
Diarrhea	2 (1)	2 (1)	3 (<1)	4 (<1)
Nausea	1 (<1)	2 (1)	2 (<1)	6 (<1)
AE leading to permanent discontinuation of study drug	2 (1)	2 (1)	15 (2)	16 (2)
Neuropsychiatric AEs leading to withdrawal	0	1 (1)	6 (<1)	4 (<1)
Any serious AE[a]	9 (6)	10 (6)	50 (7)	55 (8)

[a]2 deaths were reported (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1) in the GEMINI-2 study, including 1 in the Latin American subgroup; both were in the DTG + 3TC group and were considered unrelated to the study drug regimen.

Conclusions

- Results from GEMINI-1 and GEMINI-2 demonstrate noninferior virologic efficacy for DTG + 3TC versus DTG + TDF/FTC at Week 48
- The overall safety and tolerability profile at Week 48 was comparable among the DTG + 3TC and DTG + TDF/FTC groups
- Subgroup analysis of efficacy and safety in participants randomized and treated across Latin American sites was generally consistent with overall study results
- Both regimens were associated with low rates of CVW through Week 48, with no INSTI or NRTI mutations observed among participants meeting CVW criteria
- Changes in renal and bone biomarkers and fewer drug-related AEs support use of DTG + 3TC over DTG + TDF/FTC
- These results further demonstrate DTG+3TC as an option for initial treatment of HIV infection across different geographies, including Latin America

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Reference: 1. Cahn et al. *Lancet*. 2019;393:143-155.